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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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[REDACTED] EXAMINER

ROARK, JESSICA H

ART UNIT	PAPER NUMBER
1644	

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16

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/927,121

Applicant(s)

GOLD ET AL.

Examiner

Jessica H. Roark

Art Unit

1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 09 May 2003.
- 2a) This action is **FINAL**. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1-33 is/are pending in the application.
- 4a) Of the above claim(s) 17 is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 1-16 and 18-33 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 - a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.
- 14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
 - a) The translation of the foreign language provisional application has been received.
- 15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) Notice of References Cited (PTO-892)
- 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) Information Disclosure Statement(s) (PTO-1449) Paper No(s) 11.

- 4) Interview Summary (PTO-413) Paper No(s). _____.
- 5) Notice of Informal Patent Application (PTO-152)
- 6) Other:

DETAILED ACTION

1. Applicant's amendment, filed 5/9/03 (Paper No. 15), is acknowledged.

Claims 34-60 have been canceled.

Claims 1-33 are pending.

Acknowledgement is made of Applicant's amendment, filed 5/9/03, correcting the Brief Description of the Drawings (Figure 3A, 3B and 3C) and amending row 14 of Table 3 on page 71. The amendments have been entered.

2. Applicant's election with traverse of Group I with species elections of "VH+VL", "IgG1", "VL of a human kappa chain", "further comprising a carrier protein and a cytokine", "protein A" and "non-Hodgkin's lymphoma" in Paper No. 15 is acknowledged. The traversal is on the grounds that the methods encompassing the various species do not depend upon the detailed structure of the antibody components and because multiple methods of treatment would require only minor modifications in the method. This is not found persuasive because the structures do differ as set forth in Paper No. 13 and because each patient population is distinct, requiring distinct methodology.

However, in view of the rejections set forth below, the species requirement with respect to the isotype of the light chain and heavy chain constant regions as well as with respect to the protein used to isolate the chimeric protein, is withdrawn.

The requirement is still deemed proper and is therefore made FINAL with respect to the "VH+VL" species, the species of B cell mediated pathology, and the species of components of the composition administered (carrier protein and cytokine).

Claim 17 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim.

Claims 1-16 and 18-33 are under consideration in the instant application.

IDS

- 3 Applicant's IDS, filed 10/2/02 (Paper No. 11), is acknowledged.

Specification

4. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention *to which the claims are directed.*
5. The abstract of the disclosure is objected to because it appears to be of undue length. Applicant is reminded that MPEP 608.01(b) requires that the Abstract not exceed 150 words in length. Correction is required. See MPEP § 608.01(b).

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6. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which Applicant may become aware in the specification.

In particular, Applicant is requested to verify that if any of the vectors and related reagents are trademarked, and if to so indicate in the specification.

7. The disclosure is objected to because it contain an embedded *at least* on page 35 at line 19. Applicant is required to delete the embedded hyperlink. See MPEP § 608.01.

Applicant is requested to review the application for additional embedded hyperlinks and/or other forms of browser-executable code and delete them. Embedded hyperlinks and/or other form of browser-executable code are impermissible in the text of the application as they represent an improper incorporation by reference. See MPEP § 608.01 and 608.01(p).

Claim Rejections - 35 USC § 112 first paragraph

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-16 and 18-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for altering a B cell mediated pathology that is a non-Hodgkin's B cell lymphoma (NHL) by administering a chimeric protein comprising a VH and VL region associated with a B cell clone from a patient having said lymphoma, does not reasonably provide enablement for altering the lymphoma-associated pathology by administering only a VH or only a VL region or portions thereof, or for altering other B cell mediated pathologies. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Applicant has provided a working example in which both the VH and VL of an antibody derived from a non-Hodgkin's B cell lymphoma are used as an immunogen conjugated to KLH and in combination with GM-CSF to stimulate an immune response to the lymphoma expressing the antibody from which the VH and VL were derived (specification pages 71-73).

However the scope of the instant claims encompass altering *any* B cell mediated pathology by administering *any* fragment of an antibody VH or VL region, or by administering *only* a VH or VL region.

The state of the art recognized that the surface immunoglobulin expressed by B cells of patients with malignant B cells could be used as an immunogen to stimulate an immune response to the tumor. However, the skilled artisan was also aware that lymphoma immunotherapy required both the VH and VL be present. For example, Benvenuti et al. (Gene therapy 2000; 7:605-611, IDS) teach that even when antibodies to the lymphoma Ig have been shown to react primarily with the VH region, the VH+VL combination was still need to elicit a protective effect. Thus it is unpredictable for any given lymphoma immunoglobulin that a chimeric protein comprising only the VH, only the VL, or portions thereof, would be able to alter the B cell mediated pathology.

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Further, although the art recognized that the B cell mediated pathology of non-Hodgkin's lymphoma and certain other B cell malignancies could be altered by administering a composition comprising the VH+VL of the immunoglobulin expressed by the lymphoma conjugated to a carrier such as KLH, particularly in combination with the cytokine GM-CSF; the state of the art did not appear to recognize that this approach could be extended to other B cell mediated pathologies such as B cell-mediated autoimmune diseases. Unlike B cell malignancies which involve B cells expressing immunoglobulins having the same VH+VL pair, B cell mediated autoimmune diseases involve multiple B cells which do not necessarily share the same VH+VL pair. The disclosure does not provide any working examples showing that the approach utilized to alter the lymphoma pathology could also be applied to any other B cell mediated pathologies. Given the diverse antibodies involved in B cell autoimmune diseases, the skilled artisan would consider it highly unpredictable that the results obtained for a B cell pathologies involving only a single VH+VL could be translated to diseases involving multiple VH+VL combinations without undue experimentation.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification, and the breadth of the claims, it would require undue experimentation to practice the claimed invention as broadly claimed with respect to methods of altering any B cell mediated pathology, or for altering a B cell mediated pathology that is a non-Hodgkin's B cell lymphoma by administering only a VH region, only a VL region, or portions thereof.

Claim Rejections – 35 U.S.C. §§ 102 and 103

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

11. Claims 1-2, 4-10, 15-16 and 32-33 are rejected under 35 U.S.C. 102(e) as being anticipated by Denney, Jr. et al. (U.S. pat. No. 5,972334, see entire document), as evidenced by Chapter 139 of The Merck Manual of Diagnosis and Therapy (eds. Beers M.H. and Berkow R, Seventeenth Edition, 1999, Merck Research Laboratories, Whitehouse Station, N.J., pages 955-962).

Denney Jr. et al. teach methods of altering a B cell mediated pathology that is a B cell malignancy, including B cell lymphomas, by administering a composition comprising a multivalent vaccine (see entire document, but especially columns 3-7, 14-15, 31-33 and 53-64). Although Denny Jr. et al. do not explicitly state that the B cell lymphomas include a "non-Hodgkin's lymphoma", the ordinary artisan would immediately envisage non-Hodgkin's lymphoma in view of any teaching of "B cell lymphoma" since as evidenced by Chapter 139 of The Merck Manual, non-Hodgkin's lymphoma is the most common type of lymphoma.

Denny Jr. et al. teach that the multivalent vaccine comprises the variable regions (VH and VL) corresponding to immunoglobulin expressed by the patient's B cells, molecularly cloned and linked to constant regions (e.g., columns 53-64). Denny Jr. et al. teach that the VL may be joined to either a kappa or lambda constant region, while it is preferred that the VH be linked to either a gamma 3 or gamma 4 constant region (e.g., column 54 at lines 25-44). Although Denny Jr. et al. do not explicitly state that the variable regions are the entire variable regions or that the constant regions are human, the teachings of the primers used in Tables 1-3 indicates that the variable regions are full length and constant regions are human.

Conjugation of the chimeric protein to the carrier protein KLH is taught by Denny Jr. et al. (e.g., column 62 at lines 7-32). Denny Jr. et al. also teach that the composition may be co-administered with a cytokine, including GM-CSF (e.g., column 62 at lines 33-50).

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the vaccine administered in the method of Denny Jr. et al.

The reference teachings thus anticipate the instant claimed invention.

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 1, 3, 10-14, 18, 23-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Denney, Jr. et al. (U.S. pat. No. 5,972334), as evidenced by Chapter 139 of The Merck Manual of Diagnosis and Therapy (eds. Beers M.H. and Berkow R, Seventeenth Edition, 1999, Merck Research Laboratories, Whitehouse Station, N.J., pages 955-962) and Edelman et al. (WO96/07740, "Edelman '740") as evidenced by the English language version of WO96/07740 found in U.S. Pat. No. 6,312,690, "Edelman '690").

The claims are drawn to methods of altering the B cell mediated pathology of non-Hodgkin's lymphoma by administering a chimeric protein comprising VH+VL regions derived from a B cell clone of the patient linked to at least a portion of an immunoglobulin constant region, including wherein the constant region is a human IgG1 constant region. The claims are also directed to said method wherein the chimeric protein is produced by a method comprising isolating the encoding genes of the VH+VL and cloning the genes into a baculovirus expression vector having certain signal sequences and promotors.

Denny Jr. et al. as evidenced by Chapter 139 of the Merck manual have been discussed supra and teach a method of altering a B cell mediated pathology that is a B cell lymphoma by administering a composition comprising the VH+VL regions of a patient's B cell clone linked to VL constant regions that are either kappa or lambda and VH regions that are human gamma 3 or human gamma 4 regions. Chapter 139 of the Merck Manual evidences that any general teaching with respect to a B cell lymphoma would render obvious that method with respect to non-Hodgkin's lymphoma since non-Hodgkin's lymphoma is the most common type of lymphoma.

Denny Jr. et al. as evidenced by Chapter 139 of the Merck Manual do not teach a method of altering a B cell mediated pathology in which the VH region is linked to a human gamma 1 constant region, nor wherein any of the chimeric proteins are produced in a baculovirus expression system.

However, it would have been obvious that the chimeric protein taught by Denny Jr. et al. could be linked to a human gamma 1 constant region and that the chimeric protein could be produced by cloning in baculovirus.

Edelman et al. teach that expression of antibodies in baculovirus versus other expression systems is desirable because baculovirus permits expression of antibody without risk of viral contamination associated with isolation of antibody directly from cells of human origin, standardization of the production process, and a practically inexhaustible supply (e.g., Edelman '740 page 12 [Edelman '690 column 6, especially lines 31-40]).

Edelman et al. teach a method of cloning both the VH and VL regions of an antibody in a baculovirus vector comprising both heavy and light chain constant regions under the control of different promotors, expressing the antibody in insect cells, and isolating the resulting chimeric protein (see entire document of Edelman '740, as evidenced by the English language equivalent in Edelman '690, but especially Figure 2).

Edelman et al. teach that the VH region is linked to any human constant region, including the gamma 1 constant region, and that the VL may be joined to either a kappa or lambda constant region as (see e.g., page 5 of Edelman '740 [column 3 at lines 39 of Edelman '690]). Edelman teach and exemplify cloning an entire VH region and inserting it into an expression vector comprising the human gamma 1 constant region (see Examples 1-4, pages 12-26 of Edelman '740 [columns 6-13 of Edelman '690] and Figure 2).

Edelman et al. teach that the heavy and light chain of the antibody can be expressed from the same vector (see e.g. Figure 2) in insect cells, including the Sf9 cell line (e.g., "Example 4, pages 25-26 of Edelman '740 [column 13 of Edelman '690]). Edelman et al. also teach analysis of the expression of the protein by ELISA, and isolation of the protein using protein A (e.g., "Example 4, pages 25-26 of Edelman '740 [column 13 of Edelman '690]).

Therefore, it would have been obvious to the ordinary artisan at the time the invention was made that the method of treating a B cell lymphoma as taught by Denny Jr., et al. could be practiced by expressing the VH+VL of the patient's B cell clone using a baculovirus expression system, as taught by Edelman et al.

Denny Jr. et al. teach most aspects of the method of altering the B cell mediated pathology that is non-Hodgkin's lymphoma, except expression of the antibody in the baculovirus expression system and that constant region isotypes other than gamma 3 and gamma 4 can be used. However, Edelman et al. teach that there are several advantages to expression of an antibody using a baculovirus expression system, including standardization and an essentially "inexhaustible supply", since baculovirus expression was known in the art at the time the invention was made yield much larger quantities of protein than expression systems such as *E. coli*. Since the method of Denny Jr. et al. would potentially require multiple immunizations, the ordinary artisan at the time the invention was made would have been highly motivated to substitute the expression system taught by Edelman et al. for that of Denny Jr. et al., so that sufficient quantities of chimeric protein could be provided for use in the method of treating taught by Denny Jr. et al. Further, the ordinary artisan would also have been motivated to conjugate the antibody produced using the baculovirus system to the carrier protein KLH, as taught by Denny Jr. et al., for use in the method of Denny Jr. et al.

The ordinary artisan at the time the invention was made also would have found it obvious to utilize any number of art-recognized antibody isolation protocols to isolate any given antibody produced by the baculovirus expression system for use in the method of Denny Jr. et al. Further, since the method of Denny Jr. et al. is specific for the individual lymphoma patient, and each patient's lymphoma will be of any one of the light chain and heavy chain isotypes which can be utilized by a human antibody, the heavy and light chain isotypes used in the expression vectors can differ depending upon the isotype of the individual patient's lymphoma. Thus although in some instances it may be more appropriate to couple e VH to constant region of the gamma 3 or gamma 4 isotype, for other patients' use of a gamma 1 constant regions would be more appropriate. In addition, given a ready-made construct comprising a gamma 1 constant region, as taught by Edelman et al., the ordinary artisan would have been motivated to take advantage of this ready-made construct in any method for which a gamma 1 constant region was not contra-indicated. Depending upon the isotype of the antibody expressed, the ordinary artisan would then be motivated to utilize a purification approach most appropriate for the isotype of the antibody. Methods of using protein G versus protein A versus an anti-Ig antibody were well known in the art at the time the invention was made, as taught by Edelman et al. for protein G, and the ordinary artisan was well aware which approach was most appropriate for each isotype.

Given the teachings of Denny Jr. et al. with respect to the methods of treating a B cell lymphoma and the teachings of Edelman et al. providing method of expressing any desired antibody in a baculovirus expression system; the ordinary artisan at the time the invention was made would have had a reasonable expectation of practicing the instant method. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

14. Claims 19-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Denney, Jr. et al. (U.S. pat. No. 5,972334), as evidenced by Chapter 139 of The Merck Manual of Diagnosis and Therapy (eds. Beers M.H. and Berkow R, Seventeenth Edition, 1999, Merck Research Laboratories, Whitehouse Station, N.J., pages 955-962) and Edelman et al. (WO96/07740, "Edelman '740") as evidenced by the English language version of WO96/07740 found in U.S. Pat. No. 6,312,690, "Edelman '690") as applied to claims 1, 3, 10-14, 18, 23-33 above, and further in view of Tan et al. (Biotechnol. Appl. Biochem. 1999; 30:59-64) and Mroczkowski et al. (J. Biol. Chem. 1994; 269(18):13522-13528).

The claims are drawn to methods of treating a non-Hodgkin's B cell lymphoma utilizing a chimeric protein that is a VH+VL of an antibody and at least a part of a constant region, in which the chimeric protein is produced using a baculovirus expression system in which the vector has defined signal sequences and promoters to drive expression of both heterologous components of the antibody in the same vector.

Denny Jr. et al. as evidenced by Chapter 139 of the Merck Manual and Edelman et al. have been discussed supra and teach methods of treating a non-Hodgkin's B cell lymphoma utilizing a chimeric protein that is a VH+VL of an antibody and at least a part of a constant region, in which the chimeric protein is produced using a baculovirus expression system.

Denny Jr. and Edelman et al. do not teach the detailed components of the expression vector as recited in the instant claims.

However, Edelman et al. do teach a baculovirus expression vector in which both the VH region linked to a gamma 1 constant region and the VL region linked to a lambda constant region are expressed using the same vector (see Figure 2). In addition, Edelman et al. teach that other constant regions may be used in the vector (e.g., pages 5-6 of Edelman '740 [column 3 of Edelman '690]).

Edelman et al. also teach that expression of the VH+constant region is under control of the p10 promoter, while expression of the VL+constant region is under control of the polyhedrin (PH) promoter (Figure 2, and page 7 of Edelman '740 [columns 3-4 of Edelman '690]).

Edelman et al. also teach that any of a number of signal sequences can be used in the construct (Edelman '740 page 5 at lines 9-17 [Edelman '690 at column 3, lines 3-10]), but that the signal sequences for the VH+C and VL+C should be different (Edelman '740 page 9 at line 13 to page 10 at line 20 [Edelman '690 column 5, lines 1-40]).

Edelman et al. do not teach that the expression vector should comprise a honey bee melittin secretory signal sequence under control of the p10 promoter and a human placental alkaline phosphatase secretory signal sequence under the control of the polyhedrin promoter.

However, both the honey bee melittin signal sequence and the human placental alkaline phosphatase signal sequences were well known in the art at the time the invention was made.

Further, Tan et al. teach that the melittin signal sequence was successfully utilized in a baculovirus expression system to secrete antibody light chain (e.g., see Abstract).

In addition, Mroczkowski et al. found that secretion of heterologous proteins using a baculovirus vector comprising the human placental alkaline phosphatase single sequence resulted in even greater yields of protein in insect cells than did the honey bee melittin signal sequence, even though the alkaline phosphatase sequence was not of insect origin (e.g., see Abstract).

Therefore, in view of the teachings of Tan et al. that the honey bee melittin signal sequence was both known in the art and was known to be able to support secretion of an antibody chain, the teachings of Mroczkowski et al. that the human placental alkaline phosphatase signal peptide was also known and could support even greater secretion of heterologous proteins than the melittin signal peptide, and the teachings of Edelman et al. to use two different signal peptides to support secretion of the VH+C and VL+C antibody components; it would have been obvious to the ordinary artisan at the time the invention was made to utilize the honey bee melittin and human placental alkaline phosphatase signal sequences in the vector of Edelman et al.

The ordinary artisan would have been motivated to utilize these two particular signal peptides because Edelman et al. teach that any of a number of signal peptides could be used but that the signal peptides should be different for the VH+C and VL+C, because the melittin signal peptide had been used in similar vectors, and because the alkaline phosphatase signal peptide was known to be even better than the melittin signal peptide in supporting secretion of heterologous proteins. Given the teachings that of Edelman et al. that the identity of the signal peptide for the VH+C and the VL+C could be any of a number of signal peptides, so long as they were different; the ordinary artisan would have been motivated to prepare vectors with the melittin and phosphatase signal peptides under the control of each of the p10 and polyhedrin promotors to compare if there were any differences in the vectors and to then select the vector with the better secretion characteristics.

Given the vector of Edelman et al. in which the VH+C was already under control of the p10 promotor and the VL+C was already under control of the polyhedrin promotor, and that the melittin and alkaline phosphatase signal peptides were well known in the art for use in baculovirus expression vectors, the ordinary artisan at the time the invention was made would have had a reasonable expectation of producing a vector in which the p10 promotor controlled the melittin signal peptide linked to the VH and the polyhedrin promotor controlled the alkaline phosphatase signal peptide linked to the VL. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

15. No claim is allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jessica Roark, whose telephone number is (703) 605-1209. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number for before Final submissions is (703) 872-9306.

Jessica Roark, Ph.D.
Patent Examiner
Technology Center 1600
August 11, 2003

PHILLIP GAMBEL, PH.D
PRIMARY EXAMINER
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8/11/03